REMARKS

I. Introduction

This paper is submitted in response to the Office Action mailed January 24, 2005 for the above-identified patent application. A one (1) month extension to the time for responding to the Official Action is respectfully requested. Claims 1-39 are pending in the application. Claims 1-39 have been rejected.

Applicants have amended the first paragraph of the specification to correct an inadvertent error that was discovered in the statement of priority. In particular, the present application claims benefit to provisional application number 60/008,717 filed December 15, 1995, and not 60/008,317. The first paragraph of the specification has also been amended to reference the U.S. Patents that have issued since the filing of the present application. No new matter has been added.

II. The Rejections Under 35 U.S.C. §112 ¶1 Should Be Withdrawn

The Examiner has rejected claims 1-17 and 35-39 under 35 U.S.C. §112 ¶1, as failing to comply with the enablement requirement. The Examiner alleges that the specification, while enabling for producing a chimeric mRNA *in vitro*, does not enable the production of a chimeric RNA in a cell *in vivo*, for therapeutic treatment of human papilloma virus. The Examiner further alleges that the Applicants provide only prophetic guidance for using an *in vivo* mouse model for papilloma infections to test the PTMs of the instant invention.

However, the specification clearly discloses actual working examples of trans-splicing *in vivo* – not simply prophetic guidance for using an *in vivo* mouse model. For, example, successful *in vivo* repair of the clotting factor VIII gene using spliceosome-

mediated *trans*-splicing is explicitly described in the specification and demonstrates the feasibility of repairing factor VIII using the present invention. (*See* Specification, Example 12).

In addition, the specification describes *in vivo* trans-splicing by injecting PTM expression plasmids into the tumors of athymic (nude) mice. The tumors were established by injecting H1299 cells (human lung cancer tumors) into the dorsal flank subcutaneous space of the mouse. PTM expression plasmids were then injected into the tumors and, after 48 hours, trans-splicing was detected in 8 out of 19 PTM treated tumors, with two of the samples producing the predicted trans-spliced product (466 bp). Six additional tumors were subsequently positive for trans-splicing, after a second PCR amplification, and again produced the predicted trans-spliced product (196 bp). Each positive sample was sequenced, demonstrating that βHCG6 exon 1 was precisely trans-spliced to the coding sequence of DT-A (wild type or CRM mutant) at the predicted splice sites. (*See* Specification, paragraph 214; Table 2). Therefore, the specification clearly enables application of the presently claimed nucleic acids and cells *in vivo*.

Moreover, the Examiner states that the specification enables producing a chimeric mRNA *in vitro*. But an *in vitro* example in the specification constitutes a working example, sufficient to support enablement of the claimed nucleic acids and cells *in vivo*, if the example correlates with the claimed invention. The specification discloses PTMs and methods of using such PTMs to produce a chimeric RNA, where the PTMs comprise a target binding domain specific to a viral or papilloma viral pre-mRNA. (*See* Specification, *e.g.*, Example 13). Applicants respectfully submit that the mechanism of spliceosome-mediated *trans*-splicing to produce a chimeric RNA is the same whether it

occurs *in vivo* or *in vitro*. Indeed, the specification discloses that PTM driven *trans*-splicing occurred in a cell culture of human lung cancer line H1299 at the endogenously expressed βIICG6 exon 1 and the first nucleotide of DT-A, exactly as the *in vivo* working example described above. (*See* Specification, paragraph 212; Figure 7). As a result, one skilled in the art would recognize that the results obtained using *in vitro* models of treating human papilloma virus correlate with applications *in vivo* and, therefore, enable the claimed invention. (*See* MPEP 2164.02). In fact, Bhaumik *et al.* discloses successful *in vivo* application of PTMs targeted to human papilloma virus using the methods disclosed and claimed in the present invention. (*See* Bhaumik et al., Proc. Nat. Acad. Sci., 2004, 101:8693-98, Exhibit 1 submitted Nov. 5, 2004). Accordingly, Bhaumik *et al.* proves that the disclosed *in vitro* models correlate with the results obtained *in vivo*. And, more importantly, Bhaumik *et al.* demonstrates that the disclosure of the present invention would enable the claimed invention *in vivo*. Therefore, Applicants respectfully submit that the disclosure of the present invention would enable the production of a chimeric RNA in a cell *in vivo*, for therapeutic treatment of human papilloma virus. In view of the foregoing, and Applicants response filed November 5, 2004, reconsideration and withdrawal of the rejection of claims 1-17 and 35-39 under 35 U.S.C. §112 ¶1 is respectfully requested.

III. The Double Patenting Rejections

Claims 1-39 have been rejected under the judicially created doctrine of obviousness-type double patenting in view of claims 1-34 of U.S. Patent 6,013,487 ("the '487 Patent").

However, the judicially created doctrine of obviousness-type double patenting prohibits an Applicant from patenting the same invention more than once. Thus, a rejection based on double patenting must rely on a comparison of the claims of the issued patent to ensure that they are not directed to the same invention as that claimed in the pending application. The claims of present invention recite, *inter alia*, a nucleic acid molecule that comprises one or more target binding domains that target binding to a human papilloma virus pre-mRNA expressed within a cell. Claims 1-34 of the '487 Patent are not directed to binding domains that target binding to a human papilloma virus pre-mRNA. Thus, the presently claimed invention is not also claimed in the '487 Patent.

Furthermore, the doctrine of obviousness-type double patenting is based on the policy of preventing the unjustified or improper extension of the "right to exclude" granted by a patent. However, the present application claims priority to the '487 Patent and, therefore, has the same effective filing date as the '487 Patent (*i.e.*, December 13, 1996). Accordingly, a terminal disclaimer is not necessary since the expiration date of any granted patented would not be improperly extended.

Therefore, withdrawal of the rejection of claims 1-39 under the judicially created doctrine of obviousness-type double patenting in view of U.S. Patent No. 6,013,487 is respectfully requested.

IV. Conclusion

In view of the foregoing remarks, reconsideration and allowance of the pending claims is respectfully requested.

A one (1) month extension to the time for responding to the Official Action is respectfully requested. Payment of the extension fee is to be made according to the Credit Card Payment Form attached herewith. Applicants believe that no additional fees are required in connection with this response. However, if additional fees are required, The Commissioner is hereby authorized to charge any additional payment, or credit any overpayment, to Deposit Account No. 01-2300 **referring to Docket No. 027705.00062.**

If for any reason the Examiner determines that the application is not now in condition for allowance, it is respectfully requested that the Examiner contact the Applicant's undersigned counsel at the telephone number, indicated below, to arrange for an interview to expedite the disposition of this application.

Respectfully submitted,

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